Significant Side-Effects Requiring Change of ARV Regimen

The Experience Of The Ithemba ARV Programme, St. Mary's Hospital, Mariannhill, KZN

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Introduction

As the South African antiretroviral (ARV) programme gains momentum, there is intense media coverage and public interest regarding the potential harmful side effects of ARVs.
To address these concerns, the iThemba programme at St. Mary's hospital, Mariannhill, examined the medical records of all patients on ARVs from Feb 2003 up to to end May 2005, to identify those who developed significant side effects from treatment

Ithemba ARV Clinic,St. Mary's Hospital, Mariannhill

St Mary's Hospital

- Catchment area inner & outer Ethekwini (Durban)
- ± 750,000 people
- Antenatal clinic HIV incidence = 59% (2004)
- 200 bed community (level 1) hospital 20km west of Durban
- Catholic run, with a government subsidy
- Inpatient HIV incidence =70%

Clinic Operation

- Commenced provision of ARVs Feb, 2003
- Standard SA DOH ARV guidelines followed
- Currently 70 new patients enrolled per month
- As of May 2005, 669 patients on ART
- Medical records of all patients were reviewed – identified those who developed significant side effects from treatment,requiring drug substitution or regimen change

Regimens Used

Adults:

1a: Stavudine (d4t) 40 mg 12hly, [30 mg if <60 kg]
Lamivudine (3TC) 150 mg 12 hly
Efavirenz (EFZ) 600mg at night

1b: as above, but substitute EFV with Nevirapine (NVP) 200 mg daily x 2 weeks, then 200 mg 12hly

Regimens Used

2. AZT 300mg 12hly
   Didanosine (ddI) 400mg daily
   Lopinavir & Ritonavir (LPV/r) 3 capsules 12 hly

Children:
1: AZT + 3TC + EFZ or NVP
2: d4t + 3TC + LPV/r

Follow-up

- Patients return for follow-up weekly for first month on treatment, biweekly for next two months, and monthly thereafter. Side-effects screened for on each visit. Standard safety labs performed
- Monthly home visits conducted by home-based counselors for first 6 months of treatment
- Patients may also return to the clinic at any time if ill

Definition of Side Effects

- Significant side-effects defined as those requiring:
  - substitution of a single drug, or a change of regimen
  - discontinuation of treatment
  - or those that may have contributed to a patient's death

Grading of Side Effects

- Per clinic protocol, treatment is changed or stopped after the development of the following side effects:
  - Peripheral neuropathy:
    - Grade 3: severe discomfort/impairment, or needing narcotic analgesia
    - Grade 4: incapacitating, or not responding to narcotic analgesia

Side Effects (Continued)

- Anaemia:
  - Grade 3- Hb 6.5 – 6.9 g/dl
  - Grade 4- Hb <6.5 g/dl
- Lipodystrophy: as soon as cosmetically unacceptable to the patient - usually temporal & cheek wasting; abdominal fat deposition; breast enlargement; thigh wasting

Side Effects (Continued)

- Lactic acidosis: lactic acid level >5mmol/l with symptoms, or metabolic acidosis with raised lactate. (In 2 cases, lactic acid level not measured, but lactic acidosis suspected on basis of history & clinical presentation)
- Liver toxicity: ALT/AST >8 to 10 times normal or development of elevated bilirubin
- Psychological complaints: intolerable side effects reported by patient despite supportive measures
- Nausea/vomiting: intractable nausea or vomiting, uncontrolled by anti-emetics

Substitution of ARVs Following Side-Effects

- d4t: substituted with AZT (except in patients with pre-existing anaemia)
- AZT: substituted with d4t or LPV/r
- EFV: substituted with NVP
- Lactic acidosis or severe hepatotoxicity - all ARVs stopped for several weeks; reassessment made on individualized basis on what and when to restart

Patient Statistics

Total # of patients started Rx	669
Alive, still on treatment	627
Alive, stopped treatment	5
Died on treatment	37 (6 ARV)
Age and Gender	
Female adults	62%
Male adults	26%
Female children (≤14 years old)	6%
Male children (≤14 years old)	6%
Mean baseline CD4 count	82 cells/μL

Mean months on treatment	6.1
Patients on treatment for >6 months	235
Patients on treatment for >1 year	96

Statistics Continued

Drugs used in initial triple therapy regimens

3TC (lamivudine)	669 (100%)
EFV (efavirenz)	545 (84%)
D4t (stavudine)	540 (81%)
AZT (zidovudine)	119 (18%)
NVP (nevirapine)	101 (15%)
Lpv/r (lopinavir & ritonavir)	4 (1%)

Statistics Continued

Follow-up time

Mean months on treatment	6.1
Patients on treatment for >6 months	235
Patients on treatment for >1 year	96

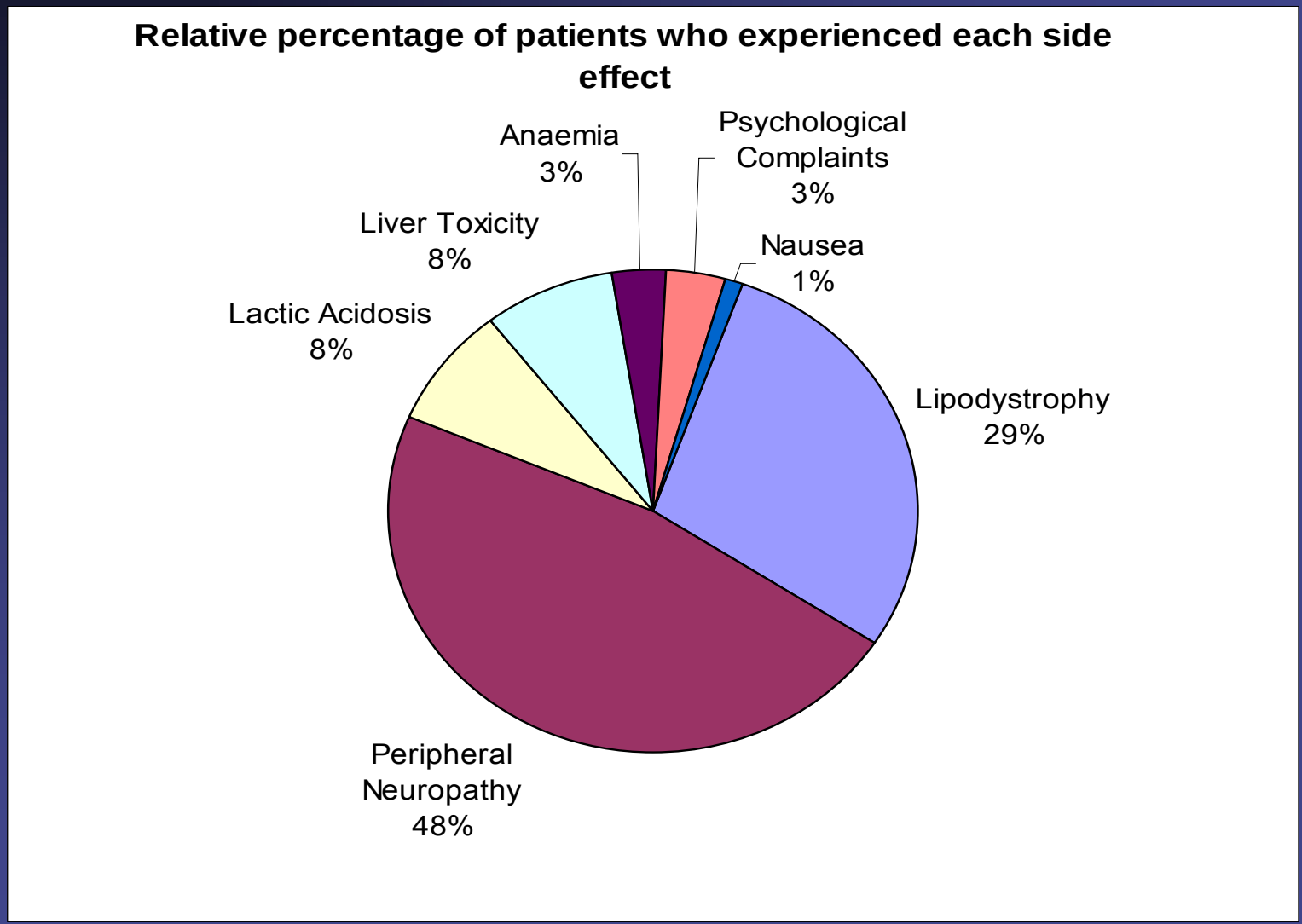
Patient deaths:

- 31 ascribable to OIs (all occurred within 12 weeks of starting Rx)
- 6 ascribable to ARVs

Findings: Side Effects and Suspected Cause

Side-effect	Suspected cause	No. of cases	Mean baseline cd4	Overall Incidence	Incidence (pts on Rx>6m)	Ave time to side-effect (m)	Deaths attributable
Peripheral Neuropathy	d4t	41	122	7.6%	15.7%	6.3	0
Lipodystrophy	d4t	25	111	4.6%	12.6%	13.9	0
Lactic acidosis	d4t	7	86	1.3%	3.0%	7.8	3
Hepatotoxicity	Mult	7	35	1.0%	1.7%	6.5	3
Anaemia	AZT	3	51	2.5%	5.3%	4.0	0
Psychological	EFV	3	66	0.6%	1.7%	3.0	0
Nausea	Mult	1	177	0.1%	-	1.9	0
Total		**87**	**93**	**13%**	**27.8%**	**6.2**	**6**

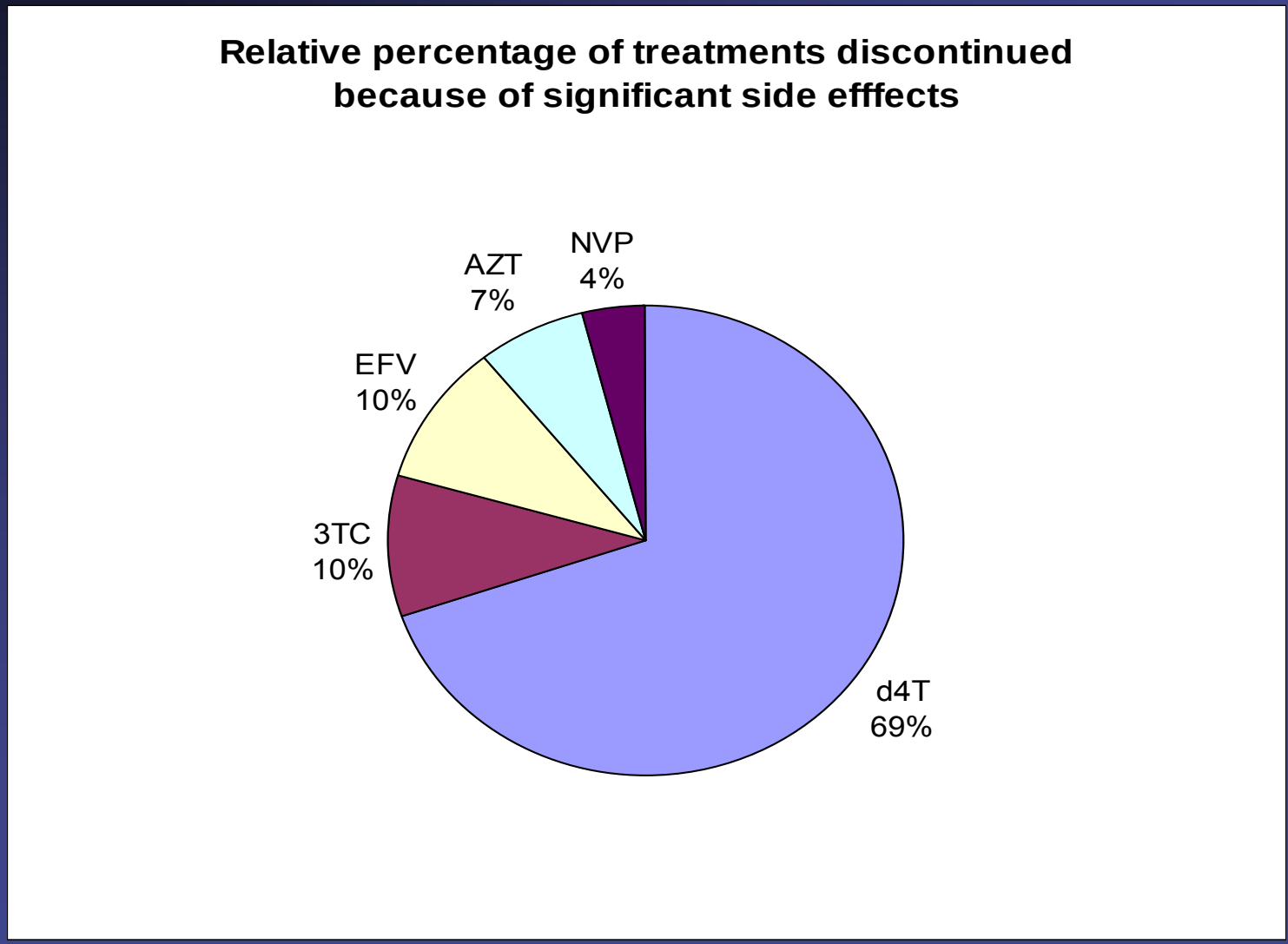
Relative Incidence of Side Effects



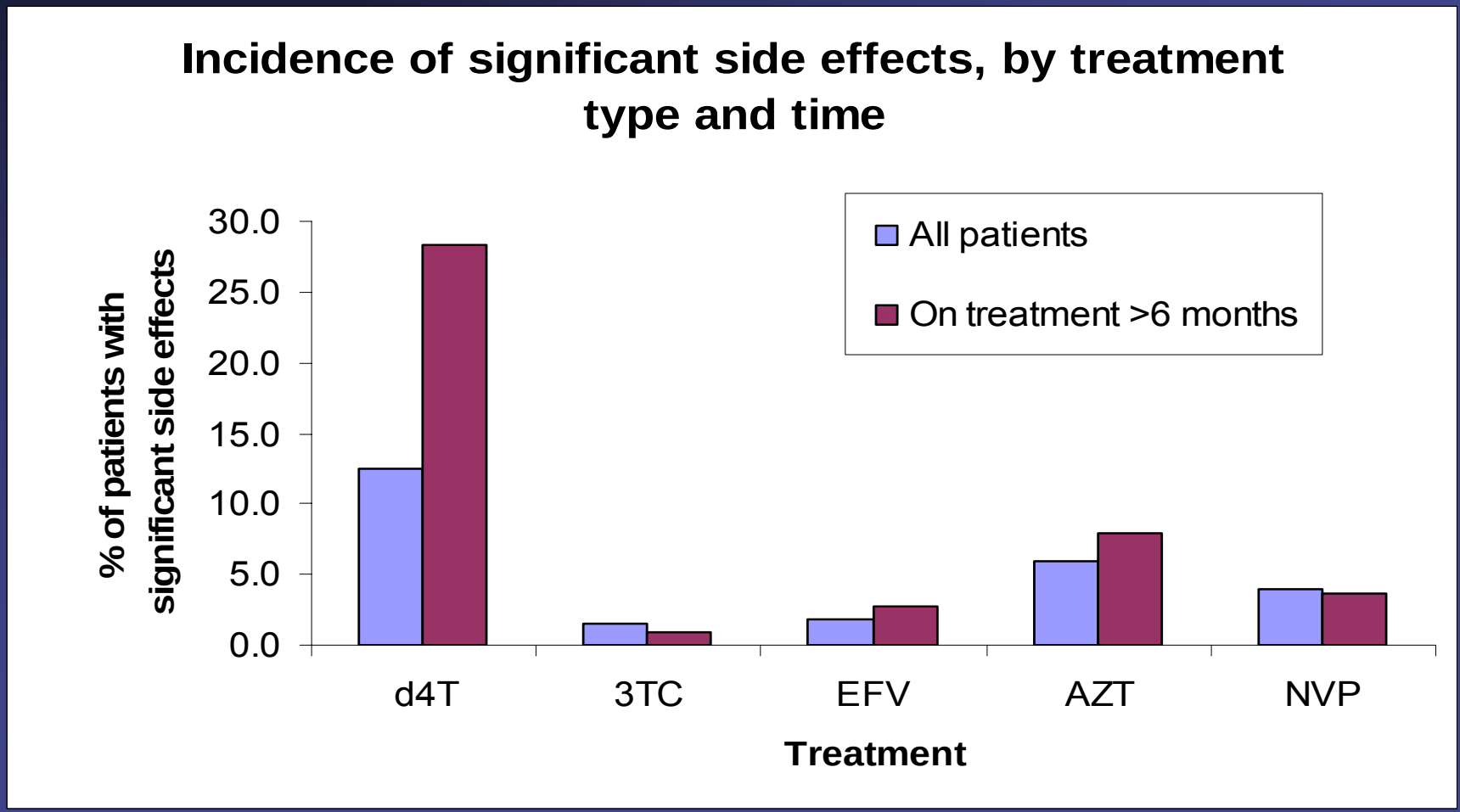
Gender

- Relative low incidence of significant side effects in adult males (10% of pts with side effects) while constituting 26% of patient population
- Adult females accounted for 86% of significant side effects (62% of patient population)
- All cases of lipodystrophy occurred in female patients
- Only 4 of the 41 cases of peripheral neuropathy occurred in males

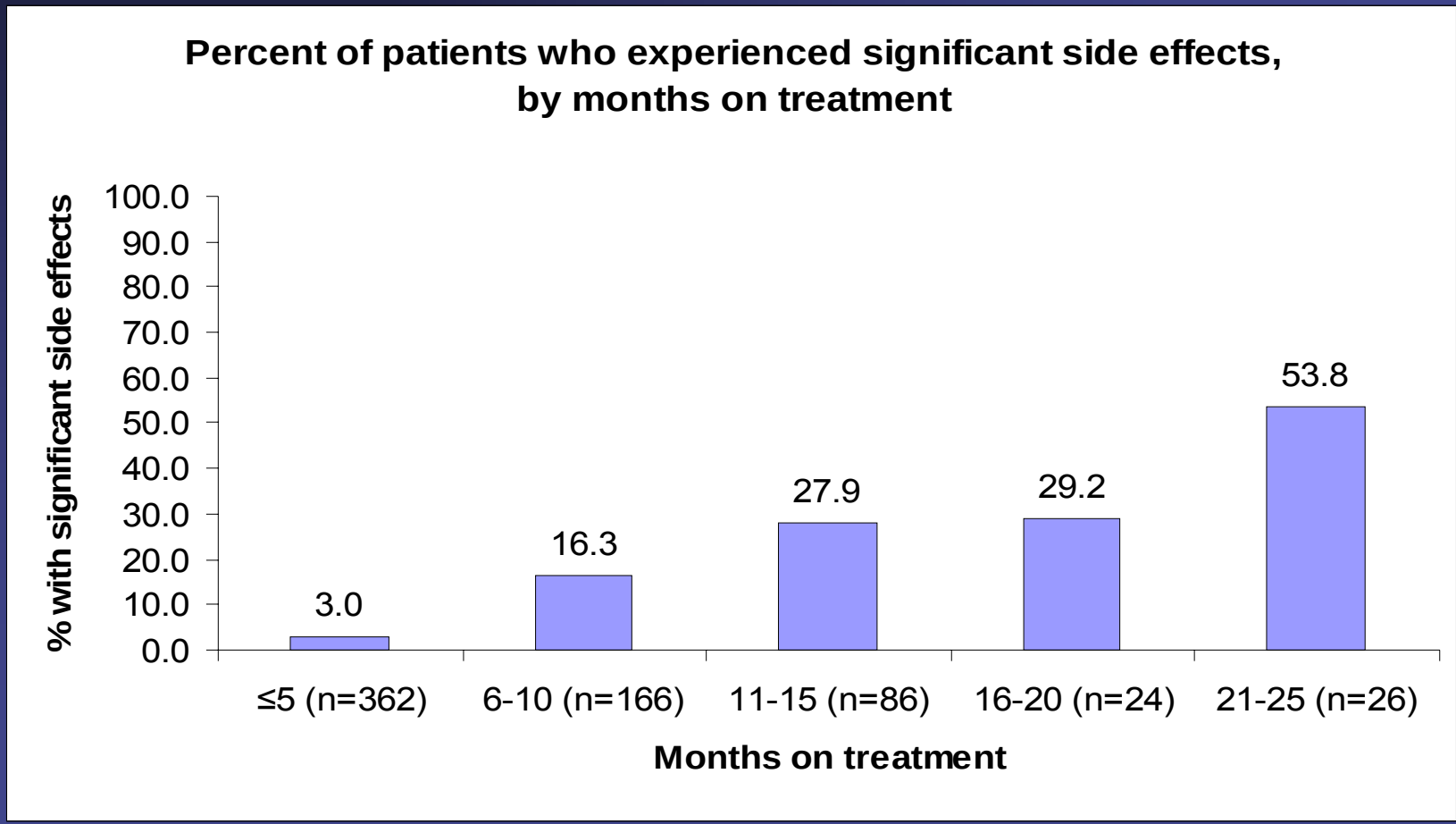
ARVs Implicated in Significant Side Effects



Incidence of Side Effects Related to ARV & Length of Treatment



Percentage of Patients With Significant Side Effects Related to Length Time on Treatment



Summary

Summary of findings:

- D4t was the main cause of side effects by far; peripheral neuropathy was the most common, followed by lipodystrophy
- Female patients seemed to be more prone to side effects, or perhaps male patients reported side effects less frequently
- After reaching about 2 years on ARV treatment, 53.8% of patients required substitution of a drug

Effect on Patient Adherence

- Despite the side effects, the number of patients who discontinued therapy was very small (0.7%), as was the incidence of ARV related deaths (0.9%)

Conclusions

- **Given the relatively high rate of side effects on d4t, urgent consideration should be given to using alternative ARVs in initial regimens, at least for high risk patients (women with BMI > 25)**
- Although side effects are not insignificant, they are rarely fatal, and with correct diagnosis and management very few patients discontinue ARV therapy
- The advantages of ARV therapy that we have observed far outweigh the disadvantages of side effects

Acknowledgements

This work would not have been possible without the help of the patients and staff at the iThemba clinic and St. Mary's Hospital